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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,832	03/15/2001	Robert A. Copeland	PH-7134	5618

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EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	**PAPER NUMBER**
1654	14

DATE MAILED: 05/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	09/808,832	COPELAND ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32 and 35-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,30 and 35-39* is/are rejected.

7)☒ Claim(s) *15-29,31 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election with traverse of the E^{cp} group and of SEQ ID NO:186 in Paper No. 8 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

2. The disclosure is objected to because of the following informalities: SEQ ID NOS must be inserted after every amino acid sequence subject to the sequence disclosure rules. See 37 CFR 1.821(d). Such sequences are present, e.g., at pages 2, 31, 32, 34-37, and 44, and throughout the Examples of the specification. Because of the number of paragraphs in the specification which will have to be amended in order to comply with this rule, Applicants are required to submit the corrections in the form of a substitute specification, including a marked-up copy, in accordance with 37 CFR 1.121(b)(3). The Sequence Listing filed June 28, 2001 lists 210 sequences. However, the examiner has not found any sequences in the specification or claims with a SEQ ID NO higher than 202. It is not clear where in the disclosure of the invention are located the amino acid sequences identified as SEQ ID NOS:203-210. Appropriate correction is required.

The substitute specification filed April 3, 2003 is not approved. The substitute specification was not submittted in accordance with 37 CFR 1.121(b)(3), e.g., was not submitted with a marked-up copy and was not submitted with a statement of no new matter. It will not be necessary to re-submit the submit specification as long as the statement of no new matter accurately identifies the substitute specification as being the one submitted on April 3, 2003.

The Sequence Listing referred to at page 21, last paragraph, of Applicants' response filed April 3, 2003 has not been received at the time of preparation of this Office action.

3. Claims 4-9 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is indefinite because when R is the group recited at page 4, last line, of the amendment filed April 3, 2003, it is not clear what is attached to the second carbonyl group present in the substituent. For analogous reasons, claim 5, page 7, line 6; and claim 30, page 17, line 5; are also indefinite.

4. Instant claims 1-32 and 35-39 are deemed not to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/189,387 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, does not disclose, e.g., all of the E^{cp} groups recited in the instant claims. Accordingly, Trouet et al (U.S. Patent No. 5,962,216) is available as prior art against the instant claims under 35 U.S.C. 102(b).

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Trouet et al (U.S. Patent No. 5,962,216). Trouet et al teach the prodrug compound Gly-Leu-Gly-Leu-DNR (see column 13, SEQ ID NO:13). The compound is hydrolyzed in the presence of MCF-7/6 (mammary carcinoma cells) conditioned medium to release daunorubicin. This compound corresponds to Applicants' claimed compound in which E^{cp} is Cap-Gly-Xp1-Xp2-Laa where Cap is R which is hydrogen. Daunorubicin is a doxorubicin analogue.

7. Claims 35-39 are rejected under 35 U.S.C. 103(a) as being obvious over Trouet et al (U.S. Patent No. 5,962,216). Application of Trouet et al is the same as in the above rejection of claims 1 and 2. Trouet et al does not teach administering the prodrug compound in combination

with a pharmaceutically acceptable carrier in order to treat breast cancer/carcinoma. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the prodrug compound of Trouet et al to treat breast cancer/carcinoma because it is desirable to treat such a disease and because Trouet et al teaches that daunorubicin, a useful therapeutic agent, is released from its prodrug form by enzymes present in breast cancer/carcinoma cells. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the prodrug of Trouet et al in combination with a pharmaceutically acceptable carrier because it is routine in the art to administer therapeutic agents in combination with pharmaceutically acceptable carriers for ease of storage, transportation, measurement, and administration. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the prodrug compound of Trouet et al to breast cancer/carcinoma cells by non-intravenous methods, e.g., by direct injection, because Trouet et al disclose that the enzymes present in blood will also hydrolyze the prodrug compound and it would be desirable to avoid premature release of the daunorubicin from the prodrug.

8. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being obvious over Trouet et al (U.S. Patent No. 5,962,216) as applied against claims 1 and 2 above, and further in view of the WO Patent Application 00/64486. More generally, Trouet et al teach a terminal group W, especially succinyl, linked through a peptide Z to a therapeutic agent M, especially doxorubicin. The peptide Z is cleaved by enzymes secreted by the target cells so as to permit entry of the therapeutic agent into the target cells. See, e.g., the Abstract; column 3, lines 11-37; column 4, lines 8-12; and claims 1, 3-6, and 12. Trouet et al do not teach a peptide Z which is cleavable by

a matrix metalloproteinase and which corresponds to Applicants' elected E^{cp} group. The WO Patent Application '486 teaches an amino acid sequence Pro-Leu-Gly-Leu-Trp-Ala which is cleaved by matrix metalloproteinases. The amino acid sequence can be used to form drug conjugates which are cleaved by the enzyme. Matrix metalloproteinases are associated with tumors and are necessary for metastasis. See, e.g., page 37, line 20 - page 38, line 6. The amino acid sequence of the WO Patent Application '486 corresponds to Applicants' elected E^{cp} group as defined in instant claims 1, 4, 5, and 10. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the prodrugs of Trouet et al using the amino acid sequence taught by the WO Patent Application '486, because Trouet et al's prodrugs can be formed using any peptide which is cleaved by an enzyme, and because the WO Patent Application '486's amino acid is sequence is described as being cleavable by an enzyme which is associated with the tumor cells which are to be treated by Trouet et al.

9. Claims 1-5 and 35-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Monsigny et al (U.S. Patent No. 4,703,107). Monsigny et al teach the anti-tumoral prodrugs PHA-Gly-Gly-L-Arg-L-Leu-Daunorubicin and PHA-Gly-Gly-L-Arg-L-Leu-Adriamycin (i.e. doxorubicin). The drugs are liberated from the prodrugs in the vicinity of tumoral cells by proteases excreted from the tumoral cells. The prodrugs can be combined with pharmaceutically acceptable carriers. See, e.g., column 1, line 61 - column 2, line 2; column 4, lines 18-24, 44, and 46; and column 6, line 67 - column 7, line 22. The prodrugs correspond to Applicants' claimed compound in which E^{cp} is Cap-Xa2-Gly-Xp1-Laa or Cap-Gly-Xp1-Xp2-Laa where Cap is R which is a polyhydroxyalkanoyl.

10. Claims 1-14 and 35-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Firestone et al (US 2002/0147138 A1). Firestone et al teach the enzyme-activated anti-tumor and anti-metastatic prodrug N-Cbz-Gly-Phe-Ala-Leu-doxorubicin. The peptide portion of the prodrug is capable of being cleaved by collagenase(IV) or elastase. The prodrugs are used to treat cancer, e.g., breast carcinoma. See, e.g., paragraphs 18, 27, 28, and 42 and claims 8-10. This prodrug corresponds to Applicants' claimed compound in which E^{cp} is Cap-Gly-Xp1-Xp2-Laa. With respect to instant claims 6-9 and 11-14, in view of the similarity in structure between the peptide portion of the prodrug of Firestone et al and Applicants' claimed E^{cp} groups, the former are deemed inherently to be cleavable by the matrixins specified in these claims. Sufficient evidence of similarity is deemed to be present between the prodrug of Firestone et al and Applicants' claimed compounds to shift the burden to Applicants to provide evidence that the claimed compounds are unobviously different than that of Firestone et al.

11. Applicant's arguments filed April 3, 2003 have been fully considered but they are not persuasive.

The rejection under 35 U.S.C. 112, second paragraph, of claims 4, 5, and 30 is maintained with respect to the issue of what is attached to the second carbonyl group present in the substituent. A carbonyl group is a divalent group. One valency is filled by covalent attachment to the phenyl group. It is not clear what fills the second valency.

The anticipation and obviousness rejections based upon Trouet et al (U.S. Patent No. 5,962,216) are maintained. Claim 1 states that Cap is an N-terminus group selected from R-, and that R is an amino capping group. Applicants have not provided any particular definition of "capping group" in the specification, and accordingly the term will be provided its plain meaning

as it would be interpreted by those of ordinary skill in the art. See MPEP 2111.01. Greenwald et al (U.S. Patent No. 6,303,569 - see column 9, lines 44-45) and Cooper et al (U.S. Patent No. 5,853,713 - see column 10, lines 40-43) show that hydrogen is a known capping group. Applicants also contend that the specification excludes the possibility that E^{cp} is Gly-Leu-Gly-Leu. The examiner was not able to find any mention of this sequence on either page 36 of the originally-filed specification or on page 36 of the substitute specification. However, in any event, limitations found only in the specification will not be read into the claims. See MPEP 2145(VI). Patentability must be based upon claimed, not unclaimed, differences over the prior art.

The obviousness rejection based upon Trouet et al (U.S. Patent No. 5,962,216) in view of the WO Patent Application 00/64486 is maintained. The Pro-Leu-Gly-Leu-Trp-Ala sequence suggested by the WO Patent Application '486 corresponds to Applicants' Paa-Xa2-Gly-Xp1-Xp2-Laa, and the succinyl suggested by Trouet et al corresponds to Applicants' Cap. Applicants argue that paragraph 0444 of the published specification (page 33, last paragraph, of the originally-filed specification) excludes the compound argued by the examiner in the rejection to be obvious. However, this paragraph of the specification does not exclude any compounds from the scope of the claims. The fact that Applicants have emphasized in the specification that certain compounds are included in the invention does not mean that all other compounds are excluded from the scope of the claims. Further, succinic acid, which is a preferred terminal group of Trouet et al, is not a polyhydroxy compound, and therefore would not be excluded even in light of this paragraph of the specification. (Applicants are correct that Trouet et al designate their terminal group as W rather than as Z as indicated in the first Office action. The rejection

has been revised to use the correct terminology. The examine regrets any confusion this error may have caused Applicants.)

The anticipation rejection based upon Monsigny et al (U.S. Patent No. 4,703,107) is maintained. The rejected claims do not contain any limitations excluding polyhydroxyalkanoyl as a capping group. Applicants argue that paragraph 0444 of the published specification (page 33, last paragraph, of the originally-filed specification) excludes the compound argued by the examiner in the rejection to be obvious. However, this paragraph of the specification does not exclude any compounds from the scope of the claims. The fact that Applicants have emphasized in the specification that certain compounds are included in the invention does not mean that all other compounds are excluded from the scope of the claims. Limitations found only in the specification will not be read into the claims. See MPEP 2145(VI). To show that Applicants' claims embrace polyhydroxyalkanoyls as the capping groups, note that in claim 1, Cap can be R-; and in claim 4, R can be R^1-C(=O)- where R^1 can be C_1-C_6alkyl substituted with 0-4 R^{1a} where R^{1a} can be -OH.

The anticipation rejection over Firestone et al (US 2002/0147138 A1) is maintained. The examiner has pointed out the structural similarity between Firestone et al's prodrug and Applicants' claimed compounds. Structural similarity is sufficient to establish prima facie anticipation. See MPEP 2112.01. The examiner agrees that Firestone et al do not use the term "matrixin". However, this does not rebut the anticipation rejection, because patentability can not be based merely upon the employment of descriptive language not chosen by the prior art. See In re Skoner, 186 USPQ 80, 82 (CCPA 1975). In any event, Firestone et al do mention a matrixin. Firestone et al teach that their peptides can be cleaved by collagenase(IV), which the

Bassiouny et al article (Circulation, Vol. 98, pages 157-163) shows is a matrix metalloproteinase and in particular is MMP-2 (see, e.g., the title of the article and page 157, paragraph bridging columns 1 and 2). Applicants contend that the Cbz of Firestone et al's prodrug is not a Cap as claimed by Applicants. However, Applicants explicitly claim that Cap can be R, and that R can be carbobenzyloxy (see, e.g., claim 10, page 10, line 15, of the amendment filed April 3, 2003).

12. Claims 15-29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 30, limited to elected SEQ ID NO, would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Claims 31 and 32, limited to the elected SEQ ID NO, are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

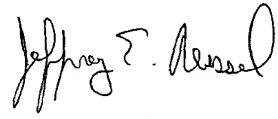
13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

May 7, 2003